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MULTILYTE LTD.

UNITED STATES DISTRICT COURT  
NORTHERN DISTRICT OF CALIFORNIA

~~SAN FRANCISCO DIVISION~~

AFFYMETRIX, INC., a Delaware corporation,  
Plaintiff and Counterdefendant,  
v.  
MULTILYTE LTD., a British corporation,  
Defendant and Counterclaimant.

Case No.: C-03-3779 WHA

**DECLARATION OF DR. LARRY J.  
KRICKA IN SUPPORT OF  
MULTILYTE LTD.'S MOTION FOR  
PARTIAL SUMMARY JUDGMENT  
FOR FURTHER CLAIM  
CONSTRUCTION OF THE TERM  
"BINDING AGENT"**

I, Larry J. Kricka, declare:

1. I submit this declaration in support of Multilyte Ltd.'s Motion for Partial Summary Judgment for Further Construction of the Term "binding agent." In particular, I have been asked to provide opinions regarding the meaning to one of ordinary skill in the art of the term "immunoassay."<sup>1</sup> I have also been asked to provide further opinions regarding the meaning of the term "binding agent" to one of ordinary skill in the art as that term is used in U.S. Patent No. 5,559,720 ("the '720 Patent"); U.S. Patent No. 5,432,099 ("the '099 Patent"); and U.S. Patent No. 5,807,755 ("the '755 Patent") (collectively "the patents-in-suit").

#### **Educational Background and Experience**

2. My educational background and experience are set out in full in my Declaration in Support of Multilyte Ltd.'s Opening Claim Construction Brief of April 4, 2004 ("Opening Declaration"). My employment history and fields of expertise are also described in my curriculum vitae, attached hereto as Exhibit A.

## The Meaning of the Term "Immunoassay"

3. One of the types of assays used by life sciences researchers to quantify or identify biological substances was often referred to in the early 1980s and continues to be referred to as a "ligand-binder assay." In my original declaration, I referred to ligand-binder assays and "binding assays;" these terms have been and continue to be understood by persons skilled in the art to be synonymous.

4. In my 1985 treatise, *Ligand-Binder Assays: Labels and Analytical Strategies*, excerpts of which are attached hereto as Exhibit B, I describe the various types of ligand-binder assays and discuss the naming conventions used to identify and distinguish different assays. In this book, I define ligand-binder assays as "[a]ssays based on the interaction or binding of a ligand with a substance which has a specific affinity for the ligand," and stated that such assays "are widely used in the biological sciences." See Ex. B at 1.

5. As I explain in my treatise, specific types of ligand-binder assays are typically

<sup>1</sup> My opinion as to the education and experience possessed by one of ordinary skill in the art in the early to mid-1980s is put forth in my Opening Declaration at ¶ 4.

1 named in a manner that indicates the type of binding agent they employ. *See Ex. B at 4.*

2       6. To demonstrate how this naming convention operates, the following chart gives  
3 examples of types of ligand-binding assays followed by the type of binding agent they employ:

<u>Type of Assay:</u>	<u>Binding Agent Employed:</u>
Immunoassay	Antibodies or antibody fragments
Receptor assay	Receptors or receptor preparations
Enzyme assay	Enzymes
DNA probe assay	DNA
RNA probe assay	RNA
Nucleic acid probe assay	Complementary nucleic acid strands
Specific binding protein assay	Specific binding protein; e.g., thyroxine binding globulin, avidin.

7. One of ordinary skill in the art would not consider a pH test to be a ligand-binder assay. Rather, a pH test employs an acid-base indicator and relies on the ionic reaction that occurs between the hydrogen ions present in the sample being tested and the acid-base indicator dye. In a ligand-binder assay, the binding agent recognizes the ligand analyte, which has a specific molecular structure; the hydrogen ions detected in a pH test do not have a molecular structure and they are not recognized by the binding agent. Rather, hydrogen ions influence the ratio of ionized and un-ionized forms of the acid-base indicator dye, as revealed by the resulting color of the mixture of ionized and un-ionized forms of the dye. Because the hydrogen ions being detected by a pH test do not have molecular structure, they cannot be labeled, as the molecular analytes in a ligand-binder assay may be and as is described in the patents-in-suit. Accordingly, a ligand-binder assay can utilize labels, which are detected to determine the presence of analytes, whereas in a pH test, the results are expressed as a color resulting from a particular ratio of ionized or un-ionized acid-base indicator dye. A pH test does not use labels. For at least these reasons, one of ordinary skill in the art would not consider a pH test to be a ligand-binder assay.

8. As with other ligand-binder assays, the term "immunoassay" derives its name from the binding agent it employs: an antibody. The prefix "immuno-" in the term "immunoassay"

1 refers to the immunogenic process whereby an antibody forms in response to an antigen.

2       9. Accordingly, to one of ordinary skill in the art, the term "immunoassay" refers to the  
3 sub-class of ligand-binder assays that exclusively employ antibodies as a binding agent.

4       10. By referring to dictionaries and learned treatises from the early 1980s, I have  
5 verified that during this time frame, one of ordinary skill in the art would have understood  
6 "immunoassay" to refer to the sub-class of ligand-binder assays that exclusively employ antibodies  
7 as a binding agent.

8       11. For example, attached hereto as Exhibit C is an excerpt from the 1983 treatise,  
9 *Immunoassays in Food Analysis*, which defined "immunoassay" in its glossary as, "[a]n assay  
10 procedure based on the reversible and non-covalent binding of an antigen by antibody using a  
11 labeled form of one or the other to quantify the system. Can be used to detect or quantify either  
12 antigens or antibodies." Ex. C at xvii.

13       12. As another example, attached hereto as Exhibit D is an excerpt from the 1990  
14 Second Edition of *A Concise Dictionary of Biology*, published by the Oxford University Press,  
15 which defined "immunoassay" as "[a]ny of various techniques that measure the amount of a  
16 particular substance by virtue of its binding antigenically to a specific antibody." Ex. D at 124.

17       13. As another example, attached hereto as Exhibit E is an excerpt from the 1982  
18 Second College Edition of *The American Heritage Dictionary*, which defined "immunoassay" as  
19 "[t]he analysis and identification of a substance on the basis of its antigenic actions." Ex. E at 644.

20       14. As another example, attached hereto as Exhibit F is an excerpt from the 1989 Second  
21 Edition of the *Oxford English Dictionary*, which defined "immunoassay" as "a bio-assay performed  
22 by means of immunological methods." Ex. F at 691.

23       15. As another example, attached hereto as Exhibit G is chapter 2 of *Immunoassays for*  
24 *the 80s*, by Dr. Roger Ekins, in which Dr. Ekins defines "immunoassay" as "an analytical method  
25 relying on the use of an antibody as the 'specific reagent.'" Ex. G at 5. The term "specific reagent"  
26 is another term for "binding agent."

27       16. By referring to patents from the early 1980s, I have also verified that in this time  
28 frame one skilled in the art would have understood "immunoassay" to refer to the sub-class of

1 ligand-binder assays that employ antibodies as a binding agent.

2       17. For example, attached hereto as Exhibit H is U.S. Patent No. 4,362,697 (issued Dec.  
3 7, 1982), which states:

4           Specific binding assays are based on the specific interaction between the ligand, i.e.,  
5 the bindable analyte under determination, and a binding partner such as an antibody.  
6 Where one of the ligand or its binding partner is an antibody and the other is a  
7 corresponding hapten or antigen, the assay is known as an immunoassay.

Ex. H at col. 1, l. 66 - col. 2, l. 4.

18. As another example, attached hereto as Exhibit I is U.S. Patent No. 4,366,243  
(issued Dec. 28, 1982), which states:

In the majority of cases, the present test device will incorporate homogeneous specific binding assay reagents which interact with the ligand or its binding capacity in the sample in an immunochemical manner. That is, there will be an antigen-antibody or hapten-antibody relationship between reagents and/or the ligand or its binding capacity in the sample. Such assays therefore are termed immunoassays and the special interaction between the labeled conjugate and its binding partner is an immunochemical binding. Thus, in such instances, the binding component of the labeled conjugate is an antigen, hapten or antibody (or a fragment thereof) and the binding partner is its corresponding immunochemical binding partner. However, it is well understood in the art that other binding interactions between the labeled conjugate and the binding partner serve as the basis of homogenous specific binding assays, including the binding interactions between hormones, vitamins, metabolites, and pharmacological agents, and their respective receptors and binding substances.

Ex. I at col. 6, ll. 8-28.

19. Today, one skilled in the art would also understand "immunoassay" to refer to the  
sub-class of ligand-binder assays that employ antibodies as a binding agent. I have verified this by  
referring to contemporary technical dictionary definitions.

20. For example, attached hereto as Exhibit J is an excerpt from the *Harmonized Terminology Database*, an authoritative resource published by the Clinical and Laboratory Standards Institute. The *Harmonized Terminology Database* provides the following definitions for immunoassay:

**immunoassay**

any laboratory method for detecting a substance by using an antibody reactive with it (RHUD.7CD)

**immunoassay**

a ligand-binding assay that uses a specific antigen or antibody capable of binding to the analyte.

21. As another example, attached hereto as Exhibit K is an excerpt from the *Glossary of*

1   *Terms Related to Pesticides*, published by the International Union of Pure and Applied Chemistry,  
2   which defines "immunoassay" in the context of pesticides as follows: "Immunoassay: Ligand-  
3   binding assay based on antibodies capable of specific binding to the pesticide analyte."

## The Meaning of "Binding Agent" in the Patents-In-Suit

5       22. My opinion as to the meaning of the term "binding agent" as it is used in the patents-  
6 in-suit is presented in my Opening Declaration and in my Reply Declaration in Support of Multilyte  
7 Ltd.'s Claim Construction Reply Brief ("Reply Declaration"). In light of the Court's claim  
8 construction order of February 22, 2005, I provide these additional opinions.

9        23. To one of ordinary skill in the art, the term "binding agent" as used in the patents in  
10 suit would be understood to encompass ligand-binder assays generally. For example, in my 1985  
11 treatise, I used the term "binder" to describe the entire class of ligand-binder assays, which includes  
12 but is not limited to immunoassays (which use antibodies as the binder, or binding agent). As such,  
13 the term "binding agent" would not be limited to assays utilizing antibodies to detect an analyte.

14        24. My understanding is based not only on the general meaning of "binding agent" to  
15 one of ordinary skill in the art, which I presented in my Opening and Reply Declarations, but also  
16 on the fact that the patents state that the inventions can use binding agents *other than antibodies*,

which necessarily means assays other than immunoassays. See, e.g., '720 Patent, col. 2, ll. 19-23,

18 || 65-58, col. 3, ll. 54-65, '099 Patent, col. 1, ll. 9-13, '755 Patent, col. 1, ll. 12-16, col. 6, ll. 28-29.

19 It also based on the fact that the '720 Patent provides examples of binding agents other than

20 antibodies, specially "binding proteins" and "receptor preparations." These binding agents are not  
21 used in immunoassays.

22        25. A "binding protein" is a protein that specifically binds to other substances, e.g., for  
23 the purpose of transport, or to reduce function, or regulate biological reactions. "Binding proteins"  
24 are not the binding agent used in immunoassays. Rather, "binding proteins" are used in specific  
25 binding protein assays.

26        26. A "receptor" is a molecular structure in or on a cell that specifically recognizes and  
27 binds to a compound and acts as a physiological signal transducer, or mediator of, an effect.

"Receptors" or "receptor preparations" are not the binding agent used in immunoassays. Rather,

1 "receptors" or "receptor preparations" are used in receptor assays.

2       27. That receptor assays and binding protein assays are distinct from immunoassays is  
3 clear from the academic literature of the time, which was frequently concerned with comparing  
4 these two types of assays.

5       28. For example, attached hereto as Exhibit L is an article from 1970 by Stephen  
6 Burstein *et al.* entitled *Demonstration by Radioligand-Binding Assay of the Structural Similarity of*  
7 *a Partially Synthetic Growth Hormone Recombinant Molecule to Its Natural Analog and to Native*  
8 *Human Growth Hormone*. This article discusses, among other things, the results of experiments  
9 conducted with seven immunoassay systems using antibodies as binding agents as compared to the  
10 results of experiments conducted with two receptor assay systems using rabbit liver membranes and  
11 rabbit mammary gland membranes as binding agents.

12       29. As another example, attached hereto as Exhibit M is an article from 1974 by David  
13 Rabinowitz *et al.* entitled *Heterogeneity of Human Luteinizing Hormone*. Among other things, this  
14 article compares the behavior of human luteinizing hormone in a radioimmunoassay system using  
15 antibodies as the binding agent to its behavior in a radioreceptor system using rat testis particulate  
16 fraction as the binding agent.

17       30. As another example, attached hereto as Exhibit N is an article from 1975 by C.Y.  
18 Lee and R.J. Ryan entitled *Radioreceptor Assay for Human Chorionic Gonadotropin*. This article  
19 describes a radioreceptor assay using a placental membrane preparation or soluble placental  
20 receptor as the binding agent that the authors claim is as sensitive as a radioimmunoassay in a  
21 particular application.

22       31. By drawing a contrast between receptor-based assays, on the one hand, and  
23 antibody-based immunoassays, on the other hand, these references reflect that one of skill in the art  
24 considers these to be different types of assays.

25       32. In the 1980s and to the present day, it was and is commonly recognized that the  
26 scientific principles underlying immunoassays are shared by ligand-binder assays generally. These  
27 underlying principles include the specific recognition of the analyte of interest by the binding agent.  
28 In addition, it has been clearly stated that ligand-binder assays "are based on the principles of

1 monitoring specific binding reactions in which the extent of binding is a function of the amount of  
 2 unknown ligand present by means of a labeled component." U.S. Patent No. 4,205,952 (filed May  
 3 10, 1977, issued June 3, 1980), Ex. R at col. 1, 11.50-54.

4       33. For example, attached hereto as Exhibit O is an excerpt from the book *Protein and*  
 5 *Polypeptide Hormones*, which is incorporated by reference into the '720 Patent. The introduction to  
 6 that book presents an equation applicable to radioimmunoassay, using "H" to represent the antigen  
 7 analyte and "Ab" to represent the antibody binding agent. The author goes on to explain that the  
 8 principle demonstrated by the equation applies to other ligand-binder assays and presents the same  
 9 equation using "S" to represent the "substance to be measured" by other ligand-binder assays and  
 10 "R" to represent the "specific reactor for S." "Specific reactor" is another term for "binding agent."  
 11 The author gives an enzyme assay as another type of assay in which the general principle would  
 12 apply. Ex. O at 4.

13       34. As another example, in *Immunoassays for the 80s*, Dr. Ekins wrote, "I propose to use  
 14 the term 'immunoassay' as representing an analytical method relying on the use of an antibody as  
 15 the 'specific reagent' whilst recognizing that many of the concepts herein discussed have a wider  
 16 applicability than to those assays which are based on antibodies *per se.*" Ex. G at 5-6.

17       35. As another example, in my Opening Declaration I discuss U.S. Patent No.  
 18 4,299,916, which is attached to that declaration as Exhibit D and attached to this declaration as  
 19 Exhibit P. I stated in my Opening Declaration, "[t]he word 'immunoassay,' which is used in the title  
 20 and throughout the '916 patent, is a word that implies the use of an antibody. Nonetheless, the '916  
 21 patent recognizes that the binding processes that are discussed in the patent are equally applicable  
 22 to nucleic acids." Opening Decl. ¶ 24; *see* Ex. P at col. 5, lines 1-7; col. 16, lines 49-53.

23       36. Although the patentee of the patents-in-suit often discusses his invention in the  
 24 context of "immunoassays," one-skilled in the art would understand the inventions to be applicable  
 25 to ligand-binder assays in general, because the patentee often states that binding agents other than  
 26 antibodies may be used, and because the patent discusses underlying scientific principles that are  
 27 applicable to ligand-binder assays in general, such as binding agents that specifically recognize the  
 analyte of interest, and monitoring specific binding reactions in which the extent of binding is a

1 function of the amount of unknown ligand present by means of a labeled component.

2       37. In the early 1980s, the binding agents listed in paragraph six, *supra*, as well as  
 3 numerous other binding agents, were used in ligand-binder assays. In my 1985 treatise *Ligand-*  
 4 *Binder Assays*, I wrote that "[o]ther binders [besides antibodies] include cell surface receptors  
 5 (Cheng, 1975); carrier or transport proteins, such as thyroxine binding globulins (Ekins 1960);  
 6 riboflavin binding protein (Lotter et al., 1982); avidin (Bayer and Wilchek, 1980); concanavalin A  
 7 (Worsfold and Hughes, 1984); protein A (Langone, 1982); and DNA (Ranki et al., 1983)." Ex. B at  
 8 7.

9       38. In particular, as I discussed in my Opening and Reply Declarations, it was  
 10 understood at the time of the patented inventions that nucleic acids, including DNA, RNA, and  
 11 oligonucleotides, could be employed as binding agents in ligand-binder assays. Opening Decl.  
 12 ¶¶ 20-24; Reply Decl. ¶ 8.

13       39. For example, attached hereto as Exhibit Q is U.S. Patent No. 4,916,075 (filed Aug.  
 14 19, 1987, issued Apr. 10, 1990), which states:

15           In the preparation of the stage of the device, a binding agent specific to the analyte is  
 16 poured into that portion of the dual insert chamber overlying area . . . [T]he choice  
 17 of macromolecular binding reactions that may be employed in the practice of this  
 18 art . . . would include any complimentary macromolecular binding reaction pair that  
 19 may be known or devised such as the specific hybridization of complimentary  
 20 strands of polynucleic acids such as DNA or RNA, etc. . . ."

21 Ex. Q at col. 5, ll. 1-4, col. 12, ll. 9-17.

22       40. As another example, attached hereto as Exhibit R is U.S. Patent No. 4,205,952 (filed  
 23 May 10, 1977, issued June 3, 1980), which states:

24           The binder is generally a high molecular weight material which has sites which  
 25 recognize specific structures. The macromolecules of greatest interest are proteins  
 26 and nucleic acid which are found in cell membranes, blood and other biological  
 27 fluids. These compounds include enzymes, antibodies, ribonucleic acid and  
 28 deoxyribonucleic acid."

Ex. R at col. 7, ll. 43-49.

41. As another example, attached hereto as Exhibit S is U.S. Patent No. 4,719,182 (filed  
 Mar. 18, 1985, issued Jan. 12, 1988), which states:

The fluorescent labels of this invention can be used as probes (also known as labels)  
 for a variety of biomedical studies and clinical chemistry determinations. They can  
 be used to label cells or other physiologically reactive species including proteins,  
 nucleic acids (e.g. DNA), enzymes and their substrates . . . and other binding

1           substances enabling the binding of such substances."

2 Ex. S at col. 3, ll. 13-23.

3         42. As another example, attached hereto as Exhibit T is U.S. Patent No. 4,943,522 (filed  
4 Aug. 10, 1988, issued Jul. 24, 1990), which states:

5           Most binding pairs employed in the invention are 'specific', e.g., antigen-antibody  
6           pairs, and other specific coupling pairs such as antibody-hapten, antibody-cell,  
7           antibody-cell fragment, RNA and DNA probes, receptor-receptor ligand, enzyme-  
8           substrate, enzyme inhibitor and other pairs in which a specific binding reaction  
9           occurs.

10          Ex. T at col. 7, ll. 38-44.

11         43. As another example, attached hereto as Exhibit U is U.S. Patent No. 4,323,647 (filed  
12 Oct. 15, 1980, issued Apr. 6, 1982), which states:

13           The receptor is always a specific binding partner for the ligand in the enzyme  
14           conjugate. For the most part, the receptors will be macromolecules which have sites  
15           which recognize specific structures. . . . The macromolecules of greatest interest are  
16           proteins and nucleic acids which are found in cell membranes, blood, and other  
17           biological fluids. These compounds include antibodies, ribonucleic acid (RNA) and  
18           deoxyribonucleic acid (DNA), and natural receptors.

19          Ex. U at col. 21, ll. 46-68.

20         44. As another example, attached hereto as Exhibit V is the 1983 article by Marjut Ranki  
21           *et al.* entitled *Nucleic Acid Sandwich Hybridization in Adenovirus Diagnosis*, which discusses the  
22           use of DNA as a binding agent. I referred to this article in my 1985 treatise when discussing the  
23           various types of binding agents used in ligand-binder assays. *See supra ¶ 38; see Ex. B at 7.*

24         45. Because DNA was understood to be a binding agent used in ligand-binder assays at  
25           the time of the patented inventions, one of ordinary skill in the art reading the patents-in-suit would  
26           understand the term "binding agent" as used in those patents to encompass DNA.

27         46. The patents-in-suit would enable one of ordinary skill in the art to practice the  
28           patented inventions with a wide variety of binding agents, including with nucleic acids, which were  
used as binding agents in ligand-binding assays at the time of the patented inventions.

29         47. As I stated above, one of ordinary skill in the art would understand the patents-in-  
30           suit to be applicable to ligand-binder assays in general. Accordingly, a construction that limited the  
31           patents to ligand-binder assays would afford the patents-in-suit their proper scope.

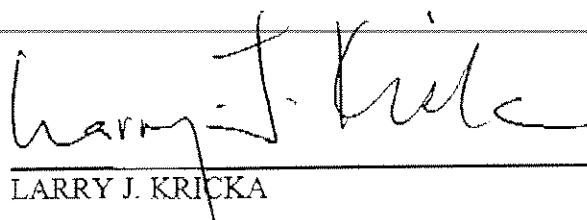
32         48. In the alternative, the patents-in-suit can be read as limited to "biological binding

1 assays." That the patents-in-suit are applicable to biological binding assays is apparent from the  
2 patent specifications. For example, the '099 and '755 patent specifications state, "the invention may  
3 be used for the assaying of analytes present in biological fluids, for example human body fluids  
4 such as blood, serum, saliva or urine." '099 Patent, col. 9, ll. 26-28; '755 Patent, col. 8, l. 66 - col. 9,  
5 l. 1. The '720 Patent states, "[t]he present invention relates to the measurement of ambient analyte  
6 concentrations in fluids, primarily the concentrations of hormones and other biologically active  
7 substances in body fluids, namely fluids present naturally in living patients, especially human  
8 beings, such as saliva, serum, blood and urine."

9 49. One of ordinary skill in the art would not consider pH tests to be biological binding  
10 assays, because they employ an acid-base indicator dye, which is a non-biological substrate,  
11 whereas biological binding assays employ biological molecules as binding agents. Moreover, as  
12 detailed in paragraph 7, *supra*, pH tests rely on the degree of ionization of the acid-base indicator  
13 dye, not on the binding of biological molecules to a binding agent. *See ¶ 7, supra.*

14 I declare under penalty of perjury under the laws of the United States that the foregoing is  
15 true and correct. Executed this 24th day of March, 2005 in Philadelphia, Pennsylvania.  
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LARRY J. KRUCKA